UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,626	03/30/2006	Jennifer Ruth Gamble	650063.402USPC	8192

500 7590 04/01/2009

SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 5400
SEATTLE, WA 98104

EXAMINER	
SGAGIAS, MAGDALINE K	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
04/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,626	GAMBLE ET AL.	
	Examiner	Art Unit	
	MAGDALENE K. SGAGIAS	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,10,13,15,21-25 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,10,13,15,25 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 2/23/09 has been entered.

Applicant's arguments filed 2/23/09 have been fully considered. The amendment has been entered. Claims 1-6, 8, 10, 13, 15, 21-25, 43 are pending. Claims 7, 9, 11-12, 14, 16-20, 27-42 are canceled. Claims 21-24, 26 are withdrawn. Claims 1-6, 8, 10, 13, 15, 25, 43 are under consideration.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8, 10, 13, 15, 25, 43 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims embrace an enormous number of sphingosine kinase functional fragments or homologs, constituting a claimed genus. The specification fails to disclose a representative number of the numerous

sphingosine kinase nucleic acid encoding fragments or homologs thereof, of any size sequence that would be able to modulate one or more mammalian endothelial cell functional characteristics in vivo. The specification does not describe the structure or functional nature of the numerous nucleic acid fragments or homologs thereof encoding sphingosine kinase that will modulate one or more mammalian cell characteristics in vivo. The specification is further silent on the specific characteristics, or sequence motifs of sphingosine kinase or homolog thereof, that may contribute to a therapeutic treatment and/or prophylaxis. The claims thus embrace a claimed genus that encompasses nucleic acid sequences or homologs thereof, yet to be discovered. As the specification fails to disclose any sphingosine kinase nucleic acid sequences or homologs thereof, the Artisan of skill could not predict that Applicant possessed any species of said sphingosine kinase nucleic acid sequences. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

> [A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

> Applicant's attention is also directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:
> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan of skill could determine the desired effect. Hence, the analysis above demonstrates that Applicant has not determined the core structure for full scope of the claimed genus. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. Therefore, the breadth of the claims as reading on numerous sphingosine kinase nucleic acid functional fragment sequences or homologs thereof, yet to be discovered; in view of the level of knowledge or skill in the art at the time of the invention, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of the genus of nucleic acid sequences encoding sphingosine kinase motifs. Thus it is concluded that the written description requirement is not satisfied for the claimed genus. In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of numerous therapeutic nucleic acid fragments of homologs thereof sequence motif, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Applicants argue that have amended claims 1-3 to recite an isolated nucleic acid molecule encoding sphingosine kinase or functional fragment or homolog thereof that comprises sphingosine kinase activity. Support for the amendment can be found throughout the specification as filed, for example, on page 18, lines 18-19.These arguments are not persuasive because on page 18 lines 18-19 cite: "Accordingly, reference to "functional level" of sphingosine kinase should be understood as a reference to the levels of sphingosine kinase activity which is present in any given cell as opposed the concentration of sphingosine kinase per se". The instant citation fails to disclose a representative number of the numerous sphingosine kinase nucleic acid encoding fragments or homologs thereof, of any size or sequence that would be able to modulate one or more mammalian endothelial cell functional characteristics.

Applicants argue that the mouse, rat, monkey, S. cerevisiae, S. pombe, A. thaliana, and O. sativa sphingosine kinase DNA and protein sequences were known prior to the effective filing date of the instant application (Pitson et al., 2002 and Kohama et al., 1998, previously made of record). Furthermore, the foregoing references identified at least five regions with an extremely high degree of sequence conservation, including the nucleotide binding site and several post-translational phosphorylation motifs (see Kohoma et al., 1998, e.g., kinase A, casein kinase II, and protein kinase C) in species from human to rice (see Figure 1, Pitson et al. 2002; Kohama et al., 1998; and Pitson et al., Biochem J. Sep 1;350 Pt 2:pp. 429-41,2000). Applicants respectfully submit that not only were numerous homologs known in the art, but, in addition, all the homologs identified possess an extremely high degree of sequence identity in the nucleotide binding domain (see abstract, Pitson et al., 2002), which is required for sphingosine kinase activity. Applicants respectfully submit that the skilled artisan would recognize the presently claimed isolated nucleic acid molecules were in possession of Applicants at the time of filing the instant specification. Moreover, nucleic acids encoding sphingosine kinase or functional

fragment or homolog thereof, wherein said kinase, functional fragment thereof, or homolog thereof comprising sphingosine kinase activity were known in the art at the time of filing the instant specification.

While the specification discloses that the sphingosine kinase homologues all possess an extremely high degree of sequence identity in the nucleotide binding domain and knowing how to generate fragments parts or fragments for example, active regions of the molecule and derivatives from insertion, deletion or substitution of amino acids of the sphingosine kinase molecule in the absence of teachings of the complete structure and function of the fragments of the gene as well as the sphingosine kinase protein encoded by the fragment of the gene, an artisan would not know what to mutate and where to mutate the gene. The claimed invention is not adequately described if the claims require essential or critical functional fragment or homologues of sphingosine kinase nucleic acid sequences which are not adequately described by the specification and which are not convention in the art at the time of filing. Possession may be shown by actual reduction to practice, or by describing the invention with sufficient relevant identifying characteristics as it relates to the claimed invention as a whole such that one of skill in the art would recognize that Applicants had possession of the invention. The specification does not provide any teachings whether such fragment would retain the function of sphingosine kinase. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, and structure/function correlation, methods of making the claimed product or any combination thereof. In this case, there is no identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide written

description of the claimed genus. The claims are extremely broad since insufficient guidance is provided as to which of the plethora of fragments of nucleic acids encode sphingosine kinase polypeptides which will retain the characteristics of a functional sphingosine kinase. While the claims are directed to fragment of nucleic acid encoding sphingosine kinase Applicants do not disclose any actual examples or prophetic examples on expected performance parameters of any of possible encoded fragments of a functional sphingosine kinase. Second a skilled artisan having knowledge of the mouse, rat, monkey, S. cerevisiae, S. pombe, A. thaliana, and O. saliva sphingosine kinase sequences and that the sphingosine kinase homologues all possess an extremely high degree of sequence identity in the nucleotide binding domain and knowing how to generate fragments parts or fragments for example, active regions of the molecule and derivatives from insertion, deletion or substitution of amino acids of the sphingosine kinase molecule will not be able to recognize that the Applicant was in possession of the claimed invention because each fragment having distinct sequence structure elicit distinct functional characteristics in the claimed sphingosine kinase molecule. The broadly claimed fragments fail to uniquely identify the structural and functional characteristics of the claimed sphingosine kinase.

Claims **1-6, 8, 10, 13, 15, 25, 43** remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for overexpression of sphingosine kinase by introducing into mammalian endothelial cells a nucleic acid encoding sphingosine kinase resulting in enhancing cell survival, altering adhesion molecule expression and enhancing neutrophil adhesion to endothelial cells and promote tube formation or the endothelial cells arrange into capillary like network in vitro, does not reasonably provide enablement for modulating one or more mammalian endothelial cell functional characteristics by way of the

claimed methods in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Independent claim 1 embraces a method of modulating one or more mammalian endothelial cell functional characteristics, said method comprising inducing over-expression of sphingosine kinase, wherein said over-expression is achieved by introducing into said cell an isolated nucleic acid molecule encoding sphingosine kinase or functional fragment or homolog thereof, wherein said kinase functional fragment thereof, or homolog, thereof comprises sphingosine kinase activity. Independent claim 2 embraces a method of modulating one or more endothelial cell functional characteristics in a mammal, said method comprising inducing over-expression of sphingosine kinase, wherein said over-expression is achieved by introducing into said cell am isolated nucleic acid molecule encoding sphingosine kinase or functional fragment or homolog thereof, wherein said kinase functional fragment thereof, or homolog, thereof comprises sphingosine kinase activity. Independent claim 3 embraces a method for the treatment and/or prophylaxis of a condition characterized by aberrant or otherwise unwanted endothelial cell functioning in a mammal, said method comprising inducing over-expression of sphingosine kinase, wherein said over-expression is achieved by introducing into said cell an isolated nucleic acid molecule encoding sphingosine kinase or functional fragment or homolog thereof, wherein said kinase functional fragment thereof, or homolog, thereof comprises sphingosine kinase activity.

The specification teaches that overexpression of sphingosine kinase by introducing an adenovirus containing sphingosine kinase enhances cell survival of human umbilical vein endothelial cells (HUVEC) in vitro (example 1). The specification also teaches that overexpression of sphingosine kinase alters adhesion molecule expression in HUVEC,

enhances neutrophil adhesion to endothelial cells and promotes tube formation or the endothelial cells arrange into a capillary like network (tubes) in vitro, (example 2). The specification speculates that said tube formation in vitro correlates to angiogenesis and angiogenesis is a characteristic feature of many chronic inflammatory diseases (specification p 61). While the specification provides teachings pertaining to the effects of overexpression of SK in cells in vitro, the specification fails to provide any relevant teachings or specific guidance or working examples with regard to overexpression of SK in vivo, by introducing a nucleic acid encoding SK, resulting in the modulation of one or more endothelial cell characteristics or in the treatment and/or prophylaxis of a condition characterized by aberrant or otherwise unwanted endothelial cell function in a mammal. The guidance provided by the instant specification fails to correlate the overexpression of SK protein in vitro to overexpression of SK in a cell in vivo resulting in the modulation of an endothelial cell functional characteristic and in treatment and/or prophylaxis of a condition in vivo. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed methods for treating and/or prophylaxis of a disease. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

The claims embrace overexpression of SK in any type of cell in vivo by way of introducing a nucleic acid encoding SK resulting in the modulation of endothelial cell characteristics or in the treatment and/or prophylaxis of a condition characterized by aberrant or unwanted endothelial cell functioning, thus falls into the realm of gene therapy. At the time of filing the art taught that gene therapy was unpredictable without undue experimentation. With regard to gene therapy, while progress has been made in recent years for gene transfer in vivo, vector targeting to desired tissues in vivo continuous to be a difficulty as supported by teaching in the art. **Gnewuch et al**, (Cell Mol Life Sci, 59: 959-1023, 2002 (IDS)) while reviewing the

status of gene therapy notes there have been several drawbacks to gene therapy including the inaccurate delivery of the gene to the desired cellular localization, the inaccurate transposition of the gene to the required place on the human genome and the lack of activity against metastasized cancer cells (p 992, 1st bridge 2nd column). Gnewuch et al, assessed gene therapy at that time is not developed to a point of predictable results in all patients (p 992, 2nd column, 2nd paragraph). **Cuvillier** (Anticancer Drugs, 18(2): 105010, 2007 (IDS)) even four years after the filing of the instant application notes sphingosine kinase controls the levels of sphingolipids having opposite effects on cell survival/death, its gene was found to be of oncogenic nature, its mRNA is overexpressed in many solid tumors, its overexpression protects cells from apoptosis and its activity is decreased during anticancer treatments (abstract). Therefore, SK appears to be a potential therapeutic target in cancer (Cuvillier, abstract). While progress has been made in recent years for in vivo gene transfer, vector targeting in vivo to be desired organs continued to be unpredictable and inefficient. For example, numerous factors complicate the gene delivery art that could not have been overcome by routine experimentation. These include, the fate of DNA vector itself, volume of distribution, rate of clearance in tissue, the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of RNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced (Eck et al , Goodman & Gilman's The Pharmacological basis of Therapeutics, McGraw-Hill, New York, NY. pp 77-101). Cell cultures, which is an n in vitro system is not directly correlatable to the treatment of a mammal which would be in vivo or in situ.

Second the claims embrace the introduction of the nucleic acid encoding SK into any type of cell in vivo resulting in the overexpression of the protein and modulating endothelial cell functional characteristics or treatment and/or prophylaxis of a condition associated with unwanted endothelial cell functioning. At the time of filing the art is teaching that it is unpredictable if any type of cell would tolerate overexpression of sphinosine kinase in vivo. **Vadas et al,** (Biochimica et Biophysica Acta, 1781: 442-447, 2008) notes that SK switches functions and whereas there is an uniformity in the analyses of the role of SphK1 in cancer and in (most) cell lines that are either immortalized or partially/fully transformed, the results in some other cell types appear to reflect a different pattern (p 445, 1st column, 2nd paragraph). For example, in endothelial cells, there is an intolerance of overexpression of SphK1 beyond several folds (p 445, 1st column, 2nd paragraph). This is in contrast to fibroblasts or other cell lines tolerating SphK1 levels more than 100 folds over normal (p 445, 1st column, 2nd paragraph). In addition, high levels of SphK1 appear to be seen in endothelial progenitor cells, with SphK1 levels dropping following the cell differentiation (p 445, 1st column, 2nd paragraph). The pattern of function is also different in the C2C12 myoblast–myocyte system where high levels of SphK1 actually cause growth arrest and myocyte differentiation, whereas decreased SphK1 is associated with an undifferentiated proliferative state (p 445, 1st column, 2nd paragraph). Lastly, in keratinocytes, high levels of S1P have been shown to inhibit keratinocyte growth and stimulate differentiation (p 445, 1st column, 2nd paragraph). In addition, at least in primary endothelial cells, very high levels of SphK1 are not tolerated (p 445, 1st column, 2nd paragraph). The delivery of a vector to target tissue culture cells does not provide guidance cited above for overcoming the obstacles on in vivo delivery because the vector does not have to pass through the complex organization of organs and tissues. Cells cultures do no mimic organs in that there is no three-dimensional structure, blood vessels, connective tissue through which the vector

would need to pass in vivo. Any data obtained from cells grown in vitro cannot be extrapolated to the in vivo situation. The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of SK gene transfer in vivo resulting in the modulation of endothelia cell in vivo or in the treatment and/or prophylaxis of a disease raised by the state of the art. The art teaches that in vivo models have served as important vehicles to explore a variety of phenotypes associated with metastatic progression and they will continue to do so until the time comes when an in vitro system is developed that faithfully replicates all of the myriad steps and challenges that disseminating tumor cells face (**Khanna et al,** (Cardiogenesis, 26(3): 513-523, 2005) (p 518, 2nd column, last paragraph). Because of the complexity of the metastatic process and the changing microenvironmental cues and interactions that a disseminated cell experiences, the development of such an in vitro assay system is unlikely in the near future (p 518, 2nd column, last paragraph). In vivo models, therefore, must continue to be an important workhorse in metastasis research. Selection of an in vivo model must be tailored to the nature of the question being asked and with full knowledge of the caveats and inadequacies of each model system (p 521, 21st column, 1st paragraph). These models, in conjunction with in vitro modeling and manipulation of tumor cells, have enabled and will continue to enable investigators to explore the critical questions that remain, including the true nature of metastatic dormancy, the role and identity of the microenvironment cues and the development of agents that can be used to prevent or treat overt metastatic disease (p 521, 21st column, 1st paragraph). The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of SK gene transfer in vivo resulting in the modulation of endothelia cell in vivo or in the treatment and/or prophylaxis of a disease raised by the state of the art. Given the lack of guidance in the specification and in view of the teachings in the art at the time of filing regarding sphingosine kinase overexpression

in vivo, and SK treatment and/or prophylaxis via SK gene therapy, the skilled artisan would require engaging in an undue amount of experimentation without a predictable degree of success to implement in the invention as claimed.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for overexpression of SK by introducing a nucleic acid encoding SK in any type of target cell resulting in the modulation of any type of endothelial cell functional characteristics and particularly resulting in the treatment and/or prophylaxis by SK gene therapy, the lack of direction or guidance provided by the specification for overexpression of SK by introducing a nucleic acid encoding SK in any type of target cell resulting in the modulation of any type of endothelial cell functional characteristics and particularly resulting in the treatment and/or prophylaxis by SK gene therapy,, the absence of working examples that correlate to for overexpression of SK by introducing a nucleic acid encoding SK in any type of target cell resulting in the modulation of any type of endothelial cell functional characteristics and particularly resulting in the treatment and/or prophylaxis by SK gene therapy, the undeveloped state of the art pertaining to for overexpression of SK by introducing a nucleic acid encoding SK in any type of target cell resulting in the modulation of any type of endothelial cell functional characteristics and particularly resulting in the treatment and/or prophylaxis by SK gene therapy, and the breadth of the claims directed to all diseases associated with aberrant or unwanted endothelial cell functioning, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Applicants argue that the specification teaches the in vitro data which could be extrapolated into in vivo. Applicants argue the Examiner contends that the delivery of a nucleic acid to tissue culture cells does not provide guidance for overcoming the obstacles of in vivo delivery, because the nucleic acid does not have to cross through the complex organization of

organs and tissues. Further, the Examiner contends that cell cultures do not mimic in vivo organs in that there is no three dimensional structure, blood vessels, or connective tissue through which the nucleic acid would be required to cross through in vivo. Applicants respectfully submit that one having ordinary skill in the art would readily appreciate that adenoviral gene delivery is targeted (e.g., direct infection, direct injection, etc.) in order to delivery a particular therapy. Applicants submit that the skill in the art of adenoviral administration is high and that one having skill in the art would not encounter undue experimentation in delivering an adenovirus to a given treatment site. Complex experimentation is not undue, and further, such experimentation is routine in the art of gene therapy as the Examiner pointed out in the Office Action issued May 3, 2007 (see Gnuwuch et al., 2002). These arguments are not persuasive because the in vitro examples do not provide guidance for the in vivo delivery of a nucleic acid molecule encoding sphingosine kinase or functional fragments or homologues thereof such that crossing of the nucleic acid the microenvironment of cell culture medium in vitro versus the tissue barriers in vivo which affect nucleic acid cell targeting. Cell culture data, of the HUVEC cells which is an in vitro system, is not directly correlatable to the modulation of endothelial cell characteristics in vivo or to the treatment and/or prophylaxis of a condition characterized by aberrant endothelial cell function in a mammal. The delivery of a nucleic acid to tissue culture cells does not provide guidance for overcoming the obstacles of in vivo delivery because the nucleic acid does not have to cross through the complex organization of organs and tissues. Cell cultures do not mimic in vivo organs in that there is no three-dimensional structure, blood vessels, connective tissue, through which the nucleic acid would be required to cross through in vivo. Cell cultures do not mimic organs in that there is no 3-D structure, blood vessels, connective tissue through which the vector would need to pass in vivo. Therefore, in view of the lack of guidance provided by the specification

and in view of the teachings in the art at the time of filing regarding tolerance of overexpression of SK in any type of cell in vivo, the skilled artisan would need to engage in an undue amount of experimentation without a predictable degree of success to implement the invention as claimed.

Applicants further submit that Duan et al., 2007, previously made of record, provides post-filing examples of the reduction to practice of adenoviral sphingosine kinase administration in mammals. In addition, the reference correlates in vitro observations to support their studies. In fact, Duan et al. expressed sphingosine adenovirus in isolated rat cardiac myocytes, isolated rat hearts, and in vivo rat hearts. In each case, the adenoviral sphingosine kinase was overexpressed (see, for example, Figures 1, 2, and 7 of Duan et al.) Furthermore, adenoviral sphingosine kinase expression in isolated rat hearts having an ischemic injury led to decreased creatine kinase expression (released during cardiac myocyte cell death) and improved the hemodynamics following reperfusion. Thus, in this aspect, in vitro cell survival of cardiac myocytes expressing sphingosine kinase adenovirus would correlate with the decrease in creatine kinase expression in isolated rat hearts expressing sphingosine kinase adenovirus (i.e., both effects are due, in part, to decreased cell death). Duan et al. also show that in vivo administration of a sphingosine kinase adenovirus to rat hearts comprising an ischemic injury increased neovascularization and improved the morphology in sphingosine kinase treated heart compared to control hearts (see, for example, Figures 7 and 8 of Duan et al.). Furthermore, Duan et al. specifically state that "[b]ecause SPK1 protects a variety of cells, including cardiac myocytes, against apoptosis induced by different stimuli, it is reasonable to predict that the protective effects of SPK1 on the heart come, at least in part, from the suppression of cell death induced by ischemia/reperfusion injury in vivo (see page 8, 2nd column, 1st full paragraph).

These arguments are not persuasive because the Duan studies are irrelevant to the instant claimed invention. This is because the instant invention claims overexpressing the SK

transgene in a cell in vivo resulting in modulating mammalian endothelial cell functional characteristics and not modulating cardiac myocytes as is demonstrated by Duan.

Applicants argue that enablement of the claimed invention does not require a demonstration that the invention may be used therapeutically. Applicant submits that the Federal Circuit has clearly established that human clinical data sufficient to gain FDA approval is not required to establish patentability.

These arguments are not persuasive because Applicants have not provided guidance as to how determining the sphingosine kinase overexpression in vitro to the in vivo resulting in modulating endothelial cell functional characteristics or the treatment and/or prophylaxis of condition associated with aberrant or unwanted endothelial cell functioning. For example as discussed above the complexity of the metastatic process and the changing microenvironmental cues and interactions that a disseminated cell experiences, the development of such an in vitro assay system is unlikely in the near future. In vivo models, therefore, must continue to be an important workhorse in metastasis research. The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of SK gene transfer in vivo resulting in the modulation of endothelia cell in vivo or in the treatment and/or prophylaxis of a disease raised by the state of the art. Applicants have not provided evidence to overcome the issue of overexpression of SK tolerability in different cell types as raised in the art. The MPEP only states the examiner cannot ask for clinical trial data regarding safety or efficacy for enablement. No such requirement is in the present record. Applicant's claims encompass overexpression of SK in vivo resulting in modulating endothelial cell functional characteristics or treatment of a disorder. Applicants have not shown such an effect in a subject. There is no enabled use for no effect.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 5, **stand** rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 15-20 of U.S. Patent No. 10275,686. Applicants argue that until time the claims are in condition for allowance, Applicants will submit a terminal disclaimer.

Claims 1-2, 5-7, 15 **stand** rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15, 17, 23, of U.S. Patent No. 09/977,217. Applicants argue that until time the claims are in condition for allowance, Applicants will submit a terminal disclaimer.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Magdalene K. Sgagias, Ph.D.
Art Unit 1632

/Anne-Marie Falk/
Anne-Marie Falk, Ph.D.
Primary Examiner, Art Unit 1632